

Diaphragm disease in advanced ovarian cancer

Pounds, Rachel; Phillips, Andrew; Kehoe, Sean; Nevin, James; Sundar, Sudha; Elattar, Ahmed; Teo, Hong Giap; Singh, Kavita; Balega, Janos

DOI:

[10.1016/j.ejogrb.2018.05.024](https://doi.org/10.1016/j.ejogrb.2018.05.024)

License:

Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

Document Version

Peer reviewed version

Citation for published version (Harvard):

Pounds, R, Phillips, A, Kehoe, S, Nevin, J, Sundar, S, Elattar, A, Teo, HG, Singh, K & Balega, J 2018, 'Diaphragm disease in advanced ovarian cancer: Predictability of pre-operative imaging and safety of surgical intervention', *European Journal of Obstetrics & Gynecology and Reproductive Biology*, vol. 226, pp. 47-53. <https://doi.org/10.1016/j.ejogrb.2018.05.024>

[Link to publication on Research at Birmingham portal](#)

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Accepted Manuscript

Title: Diaphragm disease in advanced ovarian cancer:
predictability of pre-operative imaging and safety of surgical
intervention

Authors: Rachel Pounds, Andrew Phillips, Sean Kehoe, James
Nevin, Sudha Sundar, Ahmed Elattar, Hong Giap Teo, Kavita
Singh, Janos Balega



PII: S0301-2115(18)30247-1
DOI: <https://doi.org/10.1016/j.ejogrb.2018.05.024>
Reference: EURO 10376

To appear in: *EURO*

Received date: 18-2-2018
Revised date: 13-5-2018
Accepted date: 17-5-2018

Please cite this article as: Pounds R, Phillips A, Kehoe S, Nevin J, Sundar S, Elattar A, Teo HG, Singh K, Balega J, Diaphragm disease in advanced ovarian cancer: predictability of pre-operative imaging and safety of surgical intervention, *European Journal of Obstetrics and Gynecology* (2018), <https://doi.org/10.1016/j.ejogrb.2018.05.024>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Title Page

Manuscript Title: Diaphragm disease in advanced ovarian cancer: predictability of pre-operative imaging and safety of surgical intervention

Authors:

- Rachel Pounds¹
- Andrew Phillips²
- Sean Kehoe^{1 3}
- James Nevin³
- Sudha Sundar^{1 3}
- Ahmed Elattar³
- **Hong Giap Teo⁴**
- Kavita Singh³
- Janos Balega³ (corresponding author)

¹Institute of Cancer and Genomic Sciences, University of Birmingham, Vincent Drive, Birmingham, B15 2TT, United Kingdom; 0044121 414 3344

²Department of Obstetrics and Gynaecology, Royal Derby Hospital, Uttoxeter Road, Derby DE22 3NE, United Kingdom; 00441332785693

³Pan-Birmingham Gynaecological Cancer Centre, City Hospital, Dudley Road, Birmingham, B18 7QH, United Kingdom; 0044121 507 4620

⁴**Department of Radiology, City Hospital, Dudley Road, Birmingham, B18 7QH, United Kingdom; 0044121 507 4716**

Location of study:

Pan-Birmingham Gynaecological Cancer Centre, Birmingham, West Midlands, United Kingdom

Corresponding author:

Janos Balega; Pan-Birmingham Gynaecological Cancer Centre, City Hospital, Dudley Road, Birmingham, B18 7QH, United Kingdom;

Telephone: 0044121 507 4620,

Email: janos.balega@nhs.net

Abstract

Diaphragm disease in advanced ovarian cancer: predictability of pre-operative imaging and safety of surgical intervention

Rachel Pounds, Andrew Phillips, Sean Kehoe, James Nevin, Sudha Sundar, Ahmed Elattar, Hong Giap Teo, Kavita Singh, Janos Balega

Objectives: To establish the positive predictive values of pre-operative identification with CT imaging of metastatic diaphragm disease in surgically managed cases of advanced ovarian cancer (AOC). Additionally, we have assessed the post-operative morbidity and survival following diaphragmatic surgical intervention in a large regional cancer centre in the United Kingdom.

Study design: A retrospective review of all cases of AOC with metastatic diaphragm disease surgically treated at the Pan-Birmingham Gynaecological Cancer Centre, UK between 1st August, 2007 and 29th February, 2016.

Results: A total of 536 women underwent surgery for primary AOC. **Diaphragm disease was evident intra-operatively in 215/536 (40.1%) and 85/536 women (15.9%) underwent a procedure involving their diaphragm.** Of these 85 cases, 38 peritoneal strippings (38/85, 44.7%), 31 partial diaphragmatic resections (31/85, 35.6%) and 16 electro-surgical ablations (16/85, 18.9%) were performed. There were no significant differences in post-operative complications between the three different diaphragmatic surgical groups. Of those patients who underwent peritoneal stripping or partial diaphragm resection, 12% were upstaged to stage 4B by virtue of pleural invasion.

The positive predictive value for pre-operative radiological identification of diaphragmatic disease was 78.6%. CT imaging failed to detect diaphragmatic involvement despite obvious diaphragm disease during surgery in 29.4% of cases, giving a low negative predictive value of 64.8%. The sensitivity and specificity for CT imaging in detecting diaphragm disease was 44.3% and 93.8%, respectively.

Conclusions: Diaphragmatic disease is often discovered in AOC. However, pre-operative assessment with CT imaging is not reliable in accurately detecting diaphragm involvement. Therefore, all patients with AOC should be regarded as in potential need for diaphragm surgery and their operation undertaken in cancer centres with adequate expertise in upper abdominal surgery. If there is a suspicion of diaphragm muscle invasion during diaphragmatic peritonectomy, the muscle should be partially resected. This will lead to potential upstaging of disease to stage 4B and therefore, to suitability for targeted therapy. In our Centre, the surgical removal of diaphragmatic disease did not significantly increase surgical morbidity.

Keywords: **advanced ovarian cancer, cytoreductive surgery, diaphragm metastases, diaphragmatic resection, diaphragmatic peritoneal stripping**

Introduction

Survival in advanced ovarian cancer (stage 3B, 3C and 4 ovarian, tubal and peritoneal cancer – AOC) is dependent on residual disease following cytoreductive surgery [1-3]. Eliminating all macroscopic disease in the peritoneal cavity leads to improved prognosis in AOC and therefore, complete cytoreduction (zero macroscopic residual disease) is the key surgical aim of AOC treatment [4-8]. Cytoreduction rates in AOC have increased following the addition of upper abdominal surgical procedures, thereby improving survival in patients who would otherwise be rendered suboptimally cytoreduced [2, 6, 9].

Upper abdominal metastatic disease typically occurs via transcoelomic spread, through the transfer of malignant cells in peritoneal fluid and by direct extension of disease along peritoneal surfaces [6, 10]. There is a high incidence of diaphragm involvement in AOC [7]. In the EORTC 55971 study, diaphragmatic disease was seen in 71.0% and 42.3% of women with AOC during primary and interval debulking surgery, respectively [11].

Despite the frequency of diaphragmatic disease, it remains one of the common barriers to both optimal and complete cytoreduction [4, 5, 7, 12]. Although the surgical resection of metastatic disease has been demonstrated to significantly increase 5-year survival in AOC [13], only 30% of gynaecological oncologists in the

United Kingdom would treat diaphragm involvement upon detection [14]. Diaphragmatic surgery has a crucial role in cytoreduction and has acceptable and manageable complication and morbidity rates reported in the literature [10, 15, 16].

Questions remain as to the accuracy of pre-operative identification with CT imaging of metastatic diaphragm disease. The purpose of this study was to determine the positive predictive value (PPV) of preoperative imaging as well as the proportion of CT scans with false negative results in cases who underwent cytoreductive surgery. Additionally, we have assessed the post-operative morbidity and survival following treatment in a large regional cancer centre in the United Kingdom.

Materials and Methods

A retrospective review was performed of all women with diaphragm metastasis who underwent surgery for AOC at the Pan-Birmingham Gynaecological Cancer Centre (PBGCC) between August 2007 and February 2016. Cases were identified from the centre's prospective database. Women were categorised as per the type of diaphragm surgery performed: (1) total peritonectomy with partial diaphragmatic resection, (2) total peritonectomy, (3) electrosurgical ablation/minor peritoneal resection. Patients who underwent surgery, either received (1) primary surgery followed by six cycles of adjuvant chemotherapy or (2) imaging-guided biopsy followed by three or four cycles of neoadjuvant chemotherapy (NACT) and subsequent interval debulking surgery (IDS) with three cycles of adjuvant chemotherapy. **The pre-operative CT scans for all women with AOC in our cohort were reviewed and diaphragm involvement evaluated. In those patients who underwent IDS, pre-operative CT scans were undertaken upon completion of NACT.**

Diaphragm surgery was performed via a recognised approach [17]. If the peritoneal disease was deeply invading into the muscle layer, partial diaphragmatic resection was carried out. In the small number of cases with superficially invasive peritoneal deposits, partial resection or fulguration was carried out without formal peritonectomy. All surgical specimens were assessed by gynaecological oncology histopathologists. Complete cytoreduction (R0) was achieved when there was no macroscopic disease remaining following surgery. When disease less than 1cm remained, women were classed as being optimally (R1) cytoreduced and sub-optimally

(R2) cytoreduced when residual disease was greater than 1cm. **Retroperitoneal lymph nodes were only removed if found enlarged during exploration [18].**

We determined whether there was suspicion of disease on the pre-operative imaging reported by specialist gynaecological oncology radiologists. Intra and post-operative complications were categorised as per the Dindo grading system [19]. Complications in women who underwent diaphragmatic surgery were directly compared to control patients who did not have a diaphragmatic procedure. **Cases were matched for surgery type, surgical complexity score, disease stage, age and ASA grade.**

Positive (PPV) and negative (NPV) predictive values were calculated by comparing suspicion of diaphragm disease on pre-operative imaging to histopathological confirmation of disease from surgical specimens. Categorical variables were analysed using the Chi-squared test and continuous variables were analysed using the Kruskal-Wallis test. The p-values less than 0.05 were regarded as statistically significant. The Kaplan-Meier method was used to estimate survival with survival compared using the Mantel-Cox data and was performed using IBM SPSS statistics version 22.

Results

In total, 746 women were diagnosed with AOC at the PBGCC between August 2007 and February 2016. Of these, 536 women (71.8%) underwent cytoreductive surgery. At definitive surgical intervention, diaphragmatic involvement was detected in 215 women (215/536, 40.1%). Diaphragm surgery was performed in 85 of these 215 women (85/215, 39.5%). Of the 130 women whose diaphragm disease was not surgically removed, 89.2% (116/130) were found to have widespread unresectable disease, while the remaining were unable to tolerate an ultra-radical procedure.

Overall, in our operated cohort a procedure involving the diaphragm was performed in 15.9% of women (85/536). The proportion of women who had diaphragm surgery at the PBGCC has increased over the last nine years, from 1.6% in 2007-2008 to 20.7% in 2015-2016.

Sixteen women (16/85, 18.9%) had ablation or a minor peritoneal resection of their diaphragmatic disease, 38 (38/85, 44.7%) had stripping of the whole diaphragmatic peritoneum and 31 (31/85, 36.5%) had partial

diaphragmatic resection with total peritonectomy. There was no significant difference with regards to age, BMI, histology, organ of origin, stage or grade of disease between the three diaphragm surgical groups (Table 1). As expected, those who had more aggressive diaphragmatic surgery (resection and peritoneal stripping, compared to ablation and minor procedures) had high surgical complexity scores ($P = 0.0172$). Complete cytoreduction was achieved in 77 of the 85 women (90.6%). This was independent of the type of diaphragmatic procedure undertaken. Patients were significantly more likely to achieve complete cytoreduction following diaphragm surgery compared to those who did not undergo a diaphragmatic procedure ($P < 0.001$).

Identification of diaphragmatic disease

Pre-operative CT scans were available for 507 patients. There was no evidence of diaphragm disease on both pre-operative imaging and intra-operative inspection in 274/507 cases (true negatives, 54.0%). Although diaphragmatic involvement was not suspected on imaging in a further 149 patients, it was detected intra-operatively (false negatives, 29.4%), creating a NPV of 64.8% (Table 2). Diaphragm disease was identified on the imaging of the remaining women. This was correctly identified in 66/507 women (13.0%, true positives), while 18/507 were found to have no diaphragm involvement (3.6%, false positives). This gave a PPV of 78.6%.

In 50% of cases that were incorrectly suspected of having diaphragm involvement (false positives), liver surface disease was identified adjacent to the diaphragm with no diaphragm involvement. Of those scans that failed to detect diaphragm disease (false negatives), liver involvement was evident on 20.8% of scans and disease involving both the liver and diaphragm was discovered surgically in 12.8%.

Following intra-operative identification of diaphragmatic disease, 69 women underwent diaphragm stripping or resection. Complete radiology and histology results were available for 61. Histopathological examination confirmed disease in 60 of these 61 cases (98.4%). Diaphragm involvement was correctly identified with imaging in 27/60 women (45.0%), however CT scans failed to detect disease in 33/60 cases (55.0%). In one patient, diaphragm disease was suspected on both pre-operative imaging and intra-operative inspection yet was not identified during histopathological examination. Of the 38 women who underwent peritoneal stripping, 19 (50.0%) were found to have disease infiltration through the peritoneum into deeper structures (Table 3).

Following full thickness partial diaphragm resection, eight (8/31, 25.8%) women were upstaged after pleural invasion was detected and they were identified as having stage 4B disease.

Additional procedures and post-operative morbidity

Additional surgical procedures undertaken alongside diaphragmatic surgery are described in Table 4. Along with the standard operation (total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy) and diaphragmatic surgery, additional procedures were performed in 79/85 (92.9%) women. Fifty-three (53/85, 62.4%) women had more than one additional surgical intervention.

The number of patients who suffered post-operative complications are shown in Table 4. Of the 85 patients who underwent diaphragm surgery, 27 (31.8%) did not develop any complication. Grade 3 or higher complications (Table 5). Complications specific to diaphragmatic surgery occurred in five patients (5/85, 5.9%), two of which (2/85, 2.4%) were grade 3 or higher. Three patients (3/85, 3.5%) suffered pleural effusions (one required drainage) and two (2/85, 2.4%) were diagnosed with a pneumothorax. There was no significant difference in morbidity or in diaphragm-specific complications between the different diaphragmatic surgical groups. The overall return to theatre rate was 7.1% (6/85), none of which were related to the procedures on diaphragm.

Diaphragmatic surgery cases were compared to matched control patients who did not undergo a diaphragmatic procedure (Table 6). There was no significant difference in the number or severity of complications between those that had diaphragm surgery and their matched controls ($P = 0.8728$).

There was no statistical difference in the incidence of grade 3+ complications ($P = 0.9228$) in those who underwent standard procedures plus diaphragm surgery only compared to those who had additional procedures. However, women who underwent an additional splenectomy were statistically more likely to suffer such a complication ($P = 0.0491$). Two women were readmitted to hospital within eight weeks (2/85, 2.4%). There were two cases of mortality within thirty days of diaphragm surgery (2.4%), one secondary to a pulmonary embolism and another due to pancreatitis and acute respiratory distress syndrome. Survival data was available for 83 women; the median overall survival of those with surgically treated diaphragm disease was 46.9 (95%CI

39.8-54.0) months, comparing to a median overall survival of 42.84 months for all 536 patients during our study period.

Discussion

Our cohort of 536 patients with AOC, of which 215 had diaphragm involvement and 85 underwent diaphragmatic surgery, is one of the largest published on patients managed in the UK and is the only paper with complete denominator descriptors [21]. Since advanced surgical procedures have been introduced at our Cancer Centre, the rate of diaphragmatic surgery has increased from 1.6% to 20.7%. Such trends have been also seen in our proportion of splenectomies performed previously [22]. The use of advanced surgical procedures requires both operative experience and patients where the addition of such advanced procedures will improve outcomes. Therefore, diaphragmatic surgery should not be performed in isolation, but as part of a “total surgical package” for effective cytoreduction.

The incidence and variation of the different diaphragmatic surgical procedures performed in our series differs to other published cohorts. The rates of diaphragm surgery are typically greater amongst cohorts of primary debulking cases only; expected due to increased diaphragmatic involvement in those who have not undergone neoadjuvant chemotherapy [11, 23]. Fanfani, et al. [6] describe 234 patients who underwent surgery for AOC; 37.2% had diaphragm surgery. Of these, peritonectomy was performed in 64.4% and partial resection in 14.9%, compared to 44.7% and 36.5% in our cohort, respectively. Recently, Turnbull, et al. [24] reported 64 cases of diaphragmatic surgical procedures; just 10.9% underwent a resection. With regards to electrosurgical ablation, there has been a move towards resection of disease rather than fulguration, perhaps explaining the variation in our electrosurgical ablation rate compared to others like Tsolakidis [10] and Fanfani [6], where 22% and 20.7% had coagulation alone.

However, these studies fail to describe their patient denominator data, which is essential for meaningful assessment of surgical outcomes. A more selective approach to surgical candidates will increase the diaphragmatic resection rate as only the fittest with localised disease receive surgery. The Pan-Birmingham Gynaecological Cancer Centre has a high operated patient rate of 71.8% compared to the 56% that appears standard in the UK [25]. It is likely that patients with extensive upper abdominal disease in other centres may

not receive assessment for cytoreductive surgery. We suggest that patient denominator data should be an essential criterion for any centre outcomes regarding cytoreductive surgery [21].

Complex surgical procedures are only undertaken in our Centre when it is expected that complete cytoreduction will be achieved. The R0 rate of 90.6%, with the highest rate in the diaphragm resection group (30/31, 96.8%), was not unexpected and is consistent with the literature [8, 15]. Despite most women in our cohort undergoing other surgical procedures, there was no increase in postoperative morbidity associated with the addition of diaphragmatic surgery. However, a splenectomy combined with diaphragmatic surgery demonstrated a significant increase in the number of grade 3+ complications, contrary to other reports [22].

A total of 31.8% of patients did not experience a post-operative complication following diaphragm surgery; however, it is possible that minor complications were under-reported. Our overall rate of pulmonary complications was 5.9% and compares favourably to other published series [4-7, 10, 15, 16, 26-28]. This may reflect the proportion of women having surgery after neoadjuvant chemotherapy, who are selected for such at the multi-disciplinary team meeting. Several studies [11, 21, 29-31] have demonstrated significantly lower complication rates when neoadjuvant chemotherapy is used, and our approach is now supported by the joint statement of the Society of Gynecologic Oncologists and the American Society of Clinical Oncologists [32, 33].

There is little existing data that evaluates the radiological identification of AOC. Soleymani, et al. [27] have recently reported their series of diaphragmatic surgery, performed due to suspicion following CT imaging as well as intraoperative findings. Peritoneal disease was confirmed histologically in 96% of cases, with muscle and pleural invasion in 28% and 19%, respectively. **In our cohort, radiologists under-diagnosed diaphragmatic disease: false negative results were common, resulting in a poor NPV and low sensitivity. This may be explained by the technical limitation of CT imaging, as low volume disease is not appreciated. With the absence of surrounding ascitic fluid, diaphragmatic disease applied to the adjacent liver surface could be mistaken as liver surface or subcapsular disease (examples shown in Figures 1-3). In view of this, we should retain an element of suspicion in the context of a negative scan and consider the possibility of diaphragm involvement where liver disease is evident adjacent to the diaphragm.** All AOC cytoreductive surgical cases

should be regarded as potentially ultra-radical procedures and should only be performed in adequately resourced cancer centres with availability of expertise in upper abdominal surgery.

A significant proportion of patients (12%) with obvious diaphragm disease identified during surgery were upstaged to FIGO stage 4B as disease was found on the pleural surface. We have a low threshold for diaphragm resection when peritonectomy becomes technically impeded, as this is often a sign of muscular invasion. Resection of the diaphragmatic muscle will reveal an increased percentage of patients with stage 4B disease, who in the UK would subsequently become suitable for targeted therapies.

Conclusion

Pre-operative imaging has limited value in confirming diaphragmatic disease in women presenting with AOC. As such, women undergoing surgery for AOC should be counselled as to the possibility of requiring diaphragmatic surgical procedures. Centres equipped to care for these women, with a gynaecological oncology team having the necessary surgical expertise and access to other surgical specialities if required, seems the logical place for such operations to be concentrated. When undertaken in such centres, the surgical removal of diaphragmatic disease does not increase the risk of significant post-operative morbidity. **It is essential for centres reporting outcomes to reveal the complete denominator data to allow accurate interpretation of surgical outcomes and to allow subsequent metanalysis of their data.**

Acknowledgements: No acknowledgements are to be made

References

1. Eisenkop, S.M., Friedman, R.L., and Wang, H.J. Complete cytoreductive surgery is feasible and maximizes survival in patients with advanced epithelial ovarian cancer: a prospective study. *Gynecol Oncol* 1998; 69: 103-108.
2. Chi, D.S., Eisenhauer, E.L., Zivanovic, O. et al. Improved progression-free and overall survival in advanced ovarian cancer as a result of a change in surgical paradigm. *Gynecol Oncol* 2009; 114: 26-31.

3. Colombo, P.E., Mourregot, A., Fabbro, M. et al. Aggressive surgical strategies in advanced ovarian cancer: a monocentric study of 203 stage IIIC and IV patients. *Eur J Surg Oncol* 2009; 35: 135-143.
4. Chereau, E., Rouzier, R., Gouy, S. et al. Morbidity of diaphragmatic surgery for advanced ovarian cancer: retrospective study of 148 cases. *Eur J Surg Oncol* 2011; 37: 175-180.
5. Dowdy, S.C., Loewen, R.T., Aletti, G., Feitoza, S.S., and Cliby, W. Assessment of outcomes and morbidity following diaphragmatic peritonectomy for women with ovarian carcinoma. *Gynecol Oncol* 2008; 109: 303-307.
6. Fanfani, F., Fagotti, A., Gallotta, V. et al. Upper abdominal surgery in advanced and recurrent ovarian cancer: role of diaphragmatic surgery. *Gynecol Oncol* 2010; 116: 497-501.
7. Papadia, A., and Morotti, M. Diaphragmatic surgery during cytoreduction for primary or recurrent epithelial ovarian cancer: a review of the literature. *Arch Gynecol Obstet* 2013; 287: 733-741.
8. Gouy, S., Chereau, E., Custodio, A.S. et al. Surgical procedures and morbidities of diaphragmatic surgery in patients undergoing initial or interval debulking surgery for advanced-stage ovarian cancer. *J Am Coll Surg* 2010; 210: 509-514.
9. Aletti, G.D., Dowdy, S.C., Gostout, B.S. et al. Aggressive surgical effort and improved survival in advanced-stage ovarian cancer. *Obstet Gynecol* 2006; 107: 77-85.
10. Tsolakidis, D., Amant, F., Van Gorp, T., Leunen, K., Neven, P., and Vergote, I. Diaphragmatic surgery during primary debulking in 89 patients with stage IIIB-IV epithelial ovarian cancer. *Gynecol Oncol* 2010; 116: 489-496.
11. Vergote, I., Tropé, C.G., Amant, F. et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med* 2010; 363: 943-953.
12. Einkenkel, J., Ott, R., Handzel, R., Braumann, U.D., and Horn, L.C. Characteristics and management of diaphragm involvement in patients with primary advanced-stage ovarian, fallopian tube, or peritoneal cancer. *Int J Gynecol Cancer* 2009; 19: 1288-1297.
13. Aletti, G.D., Dowdy, S.C., Podratz, K.C., and Cliby, W.A. Surgical treatment of diaphragm disease correlates with improved survival in optimally debulked advanced stage ovarian cancer. *Gynecol Oncol* 2006; 100: 283-287.
14. Barton, D.P., Adib, T., and Butler, J. Surgical practice of UK gynaecological oncologists in the treatment of primary advanced epithelial ovarian cancer (PAEOC): a questionnaire survey. *Gynecol Oncol* 2013; 131: 347-351.
15. Tsolakidis, D., Amant, F., Van Gorp, T., Leunen, K., Neven, P., and Vergote, I. The role of diaphragmatic surgery during interval debulking after neoadjuvant chemotherapy: an analysis of 74 patients with advanced epithelial ovarian cancer. *Int J Gynecol Cancer* 2010; 20: 542-551.
16. Zapardiel, I., Peiretti, M., Zanagnolo, V. et al. Diaphragmatic surgery during primary cytoreduction for advanced ovarian cancer: peritoneal stripping versus diaphragmatic resection. *Int J Gynecol Cancer* 2011; 21: 1698-1703.
17. Eisenhauer EL, Chi DS. Liver mobilization and diaphragm peritonectomy/resection. *Gynecol Oncol* 2007; 104: 25-28.

18. Panici, P.B., Maggioni, A. Hacker, N. et al. Systematic aortic and pelvic lymphadenectomy versus resection of bulky nodes only in optimally debulked advanced ovarian cancer: a randomised clinical trial. *J Natl Cancer Inst* 2005; 20; 97(8):560-6.
19. Dindo, D., Demartines, N., and Clavien, P.A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; 240: 205-213.
20. Aletti GD, Dowdy SC, Podratz KC, et al. Relationship among surgical complexity, short-term morbidity, and overall survival in primary surgery for advanced ovarian cancer. *Am J Obstet Gynecol* 2007;197(6):676.e1-7.
21. Phillips, A., Balega, J., Nevin, J. et al. Reporting 'Denominator' data is essential for benchmarking and quality standards in ovarian cancer. *Gynecol Oncol* 2017; 146(1):94-100.
22. Phillips, A., Pounds, R., Balega, J. et al. Histopathological correlation of splenic disease with radiological and surgical findings: should we incorporate splenectomy into standard procedures for disseminated Mullerian adenocarcinoma? *Eur J Gynaecol Oncol* 2016; 37: 678-684.
23. Harter, P., Muallem, Z.M., Buhrmann, C. et al. Impact of a structured quality management program on surgical outcome in primary advanced ovarian cancer. *Gynecol Oncol* 2011; 121: 615-619.
24. Turnbull, H.L., Akrivos, N., Wemyss-Holden, S. et al. The impact of ultra-radical surgery in the management of patients with stage IIIC and IV epithelial, ovarian, fallopian tube, and peritoneal cancer. *Arch Gynecol Obstet* 2017; 295: 681-687.
25. Barclay, M., Gildea, C., Poole, J. et al. Factors affecting short-term mortality in women with ovarian, tubal, or primary peritoneal cancer: population-based cohort analysis of English National Cancer Registration Data. *Int J Gynecol Cancer*. 2016; 26(1): 56-65.
26. Ye, S., He, T., Liang, S. et al. Diaphragmatic Surgery and Related Complications In Primary Cytoreduction for Advanced Ovarian, Tubal, and Peritoneal Carcinoma. *BMC Cancer* 2017; 17: 317.
27. Soleymani, M.H., Ferrari, F., Manek, S. et al. Diaphragmatic peritonectomy vs. full thickness resection with pleurectomy during Visceral-Peritoneal Debulking (VPD) in 100 consecutive patients with stage IIIC-IV ovarian cancer: A surgical-histological analysis. *Gynecol Oncol* 2016; 140: 430-435.
28. Pathiraja, P.N., Garruto-Campanile, R., and Tozzi, R. Diaphragmatic peritonectomy versus full thickness diaphragmatic resection and pleurectomy during cytoreduction in patients with ovarian cancer. *Int J Surg Oncol* 2013; 2013: 876150.
29. Kehoe, S., Hook, J., Nankivell, M. et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. *Lancet* 2015; 18; 386(9990): 249-257.
30. Fagotti, A., Ferrandina, G., Vizzielli, G. et al. Phase III randomised clinical trial comparing primary surgery versus neoadjuvant chemotherapy in advanced epithelial ovarian cancer with high tumour load (SCORPION trial): Final analysis of peri-operative outcome. *Eur J Cancer* 2016; 59: 22-33.

31. Onda, T., Satoh, T., Saito, T. et al. Comparison of treatment invasiveness between upfront debulking surgery versus interval debulking surgery following neoadjuvant chemotherapy for stage III/IV ovarian, tubal, and peritoneal cancers in a phase III randomised trial: Japan Clinical Oncology Group Study JCOG0602. *Eur J Cancer* 2016; 64: 22-31.
32. Wright, A.A., Bohlke, K., Armstrong, D.K. et al. Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline. *Gynecol Oncol* 2016; 143: 3-15.
33. Wright, A.A., Bohlke, K., Armstrong, D.K. et al. Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2016; 1;34: 3460-3473.

Figures

Figure 1. (a) Pre-chemotherapy coronal CT image of the abdomen in a patient with high grade serous mullerian adenocarcinoma of the ovary shows metastatic nodules (white arrows) involving the right hemidiaphragm. There is also a plaque-like metastasis on the under-surface of the left hemidiaphragm (black arrow). The presence of ascites (yellow star) enables easier visualisation of the diaphragmatic metastases as separate from the adjacent liver surface. **(b)** Coronal CT image post 3-cycle neoadjuvant chemotherapy shows partial treatment response with residual diaphragmatic disease (black and white arrows). The ascites has resolved.

Figure 2. (a) Coronal and **(b)** right para-median sagittal CT images of the abdomen in a patient with stage 4 ovarian cancer post 3-cycle chemotherapy show a persistent bulky subphrenic metastasis (white star) with invasion of the liver parenchyma (black star). The mass is broad-based against and not separable from the right hemidiaphragm on CT imaging, which is surgically confirmed diaphragmatic disease.

Figure 3. Axial CT image of the upper abdomen in a patient presenting with a bulky irregular solid adnexal mass and large volume ascites. There are nodular soft-tissue abnormalities (white arrows) on the under-surface of the right hemidiaphragm consistent with metastatic deposits, which are seen separately from the liver surface.



a.

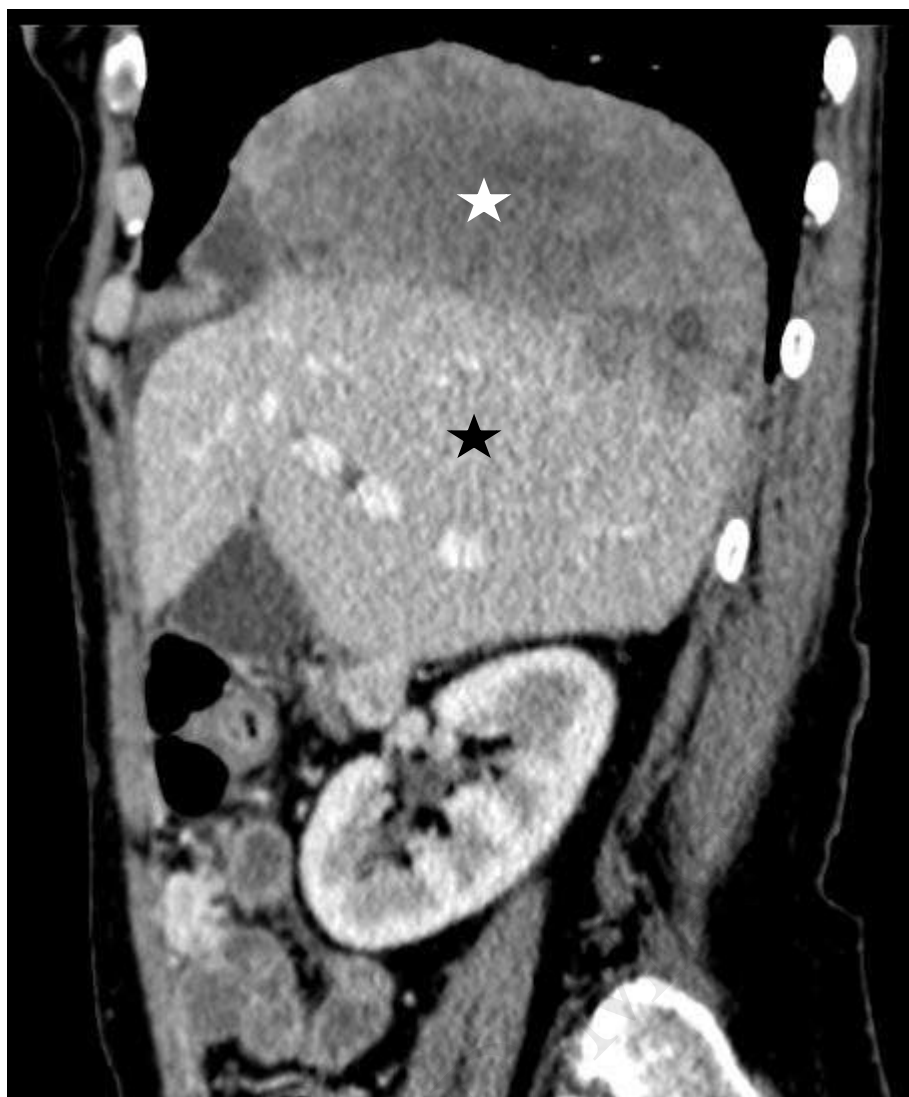


b.

Figure 1(a) Pre-chemotherapy coronal CT image of the abdomen in a patient with high grade serous mullerian adenocarcinoma of the ovary shows metastatic nodules (white arrows) involving the right hemidiaphragm. There is also a plaque-like metastasis on the under-surface of the left hemidiaphragm (black arrow). The presence of ascites (yellow star) enables easier visualisation of the diaphragmatic metastases as separate from the adjacent liver surface. **(b)** Coronal CT image post 3-cycle neoadjuvant chemotherapy shows partial treatment response with residual diaphragmatic disease (black and white arrows). The ascites has resolved.



a.



b.

Figure 2(a) Coronal and **(b)** right para-median sagittal CT images of the abdomen in a patient with stage 4 ovarian cancer post 3-cycle chemotherapy show a persistent bulky subphrenic metastasis (white star) with invasion of the liver parenchyma (black star). The mass is broad-based against and not separable from the right hemidiaphragm on CT imaging, which is surgically confirmed diaphragmatic disease.

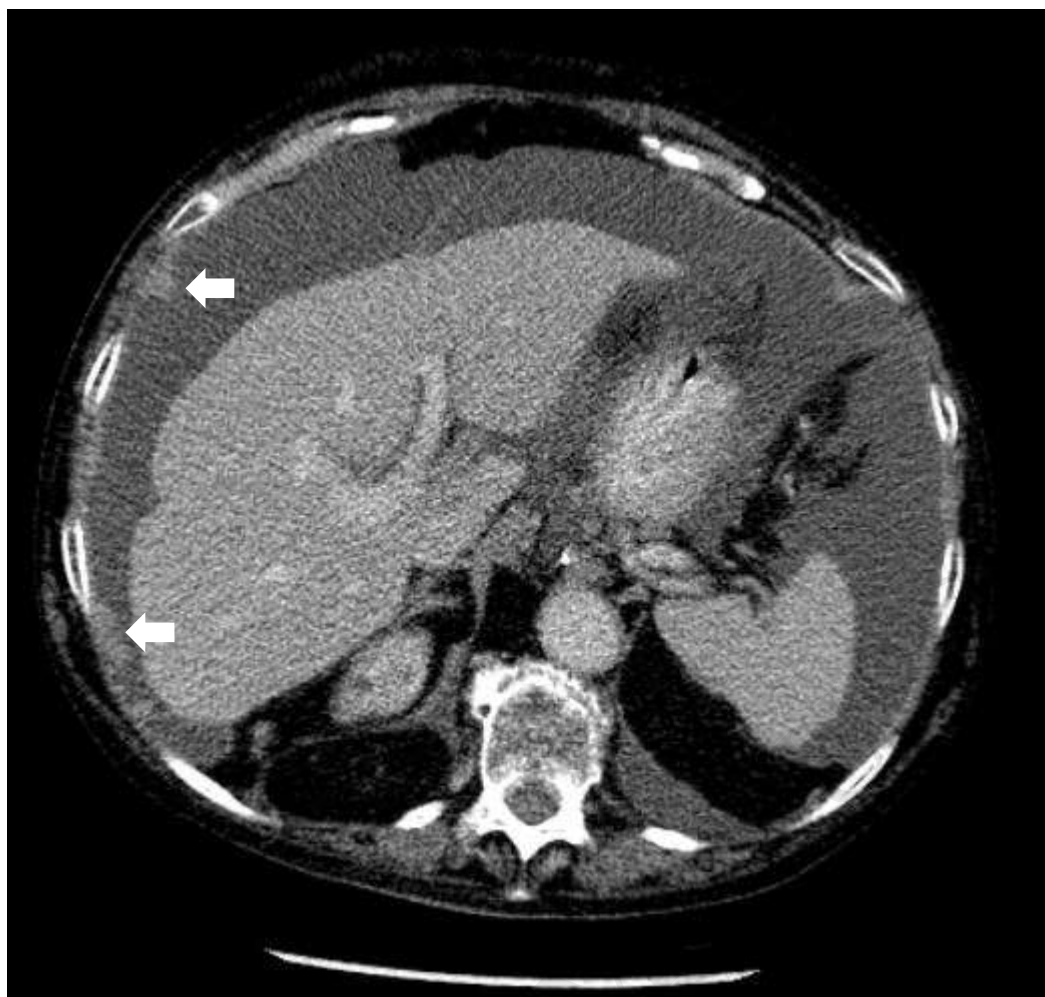


Figure 3 Axial CT image of the upper abdomen in a patient presenting with a bulky irregular solid adnexal mass and large volume ascites. There are nodular soft-tissue abnormalities (white arrows) on the under-surface of the right hemidiaphragm consistent with metastatic deposits, which are seen separate from the liver surface.

Tables

- Table 1: Population characteristics, pathology results and surgical outcomes
- Table 2: Identification of diaphragm disease
- Table 3: Distribution of diaphragm disease in patients who underwent diaphragm resection and peritoneal stripping
- Table 4: Surgical procedures and associated morbidity

- Table 5: Details of grade 3 and 4 complications following diaphragm surgery

- Table 6: Morbidity in patients following diaphragmatic surgery compared to matched controls

Tables

Table 1: Population characteristics, pathology results and surgical outcomes

	Diaphragmatic resection N=31 (36.5%)	Peritoneal stripping N=38 (44.7%)	Ablation N=16 (18.9%)	P Value	Rest of patients N=451
Age (years) (Mean \pm SD)	58.6 \pm 10.1	60.3 \pm 9.5	62.0 \pm 12.8	0.3679	63.5 \pm 2.38
ASA (Median \pm IQR)	2 (1.5-2)	2 (2-3)	2 (2-2.5)	0.3230	2 (2-3)
BMI (Median \pm IQR)	25.5 (23-28.5)	25.5 (21-28.5)	26 (22-29)	0.3679	26 (22-29)
Stage	n (%)	n (%)	n (%)	0.0305	n (%)
3B	1 (3.2)	2 (5.3)	4 (25.0)		56 (12.4)
3C	15 (48.4)	29 (76.3)	8 (50.0)		289 (64.1)
4	15 (48.4)	7 (18.4)	4 (25.0)		106 (23.5)
Organ of Origin	n (%)	n (%)	n (%)	0.8312	n (%)
Ovary	16 (51.6)	27 (71.1)	11 (68.8)		318 (70.5)
Peritoneum	3 (9.7)	4 (10.5)	2 (12.5)		78 (17.3)
Fallopian Tube	12 (38.7)	7 (18.4)	3 (18.8)		55 (12.2)
Grade	n (%)	n (%)	n (%)	0.4473	n (%)
Low (G1)	2 (6.5)	4 (10.5)	0 (0.0)		17 (3.8)
High (G2-3)	29 (93.5)	34 (89.5)	16 (100.0)		434 (96.2)
Histological Sub-type	n (%)	n (%)	n (%)	0.2642	n (%)
Serous	28 (90.3)	35 (92.1)	15 (93.8)		391 (86.7)
Clear cell	0 (0.0)	0 (0.0)	1 (6.3)		20 (4.4)
MMT	3 (9.7)	2 (5.3)	0 (0.0)		28 (6.2)
Undifferentiated	0 (0.0)	1 (2.6)	0 (0.0)		12 (2.7)
Surgery Type	n (%)	n (%)	n (%)	0.3768	n (%)
Primary	12 (38.7)	12 (31.6)	8 (50.0)		153 (33.9)
IDS	19 (61.3)	26 (68.4)	8 (50.0)		298 (66.1)
Cytoreduction	n (%)	n (%)	n (%)	0.5543	n (%)
R0	30 (96.8)	34 (89.5)	13 (81.3)		275 (61.0)
R1	1 (3.2)	3 (7.9)	2 (12.5)		67 (14.9)
R2	0 (0.0)	1 (2.6)	1 (6.3)		109 (24.2)
Surgical complexity*	n (%)	n (%)	n (%)	0.0172	n (%)
Low	2 (6.5)	2 (5.3)	5 (31.3)		352 (78.0)
Intermediate	10 (32.3)	19 (50.0)	6 (37.5)		83 (18.4)
High	19 (61.3)	17 (44.7)	5 (31.3)		16 (3.5)

* Surgical complexity as per Aletti's surgical complexity score [20].

Table 2: Identification of diaphragm disease with pre-operative imaging

Disease identification	Evidence intra-operatively	No evidence intra-operatively	Predictive Value
Suspicion on pre-operative imaging	66/507 (13.0%)	18/507 (3.6%)	PPV: 78.6% (66/84)
No suspicion on pre-operative imaging	149/507 (29.4%)	274/507 (54.0%)	NPV: 64.8% (274/423)

Table 3: Distribution of diaphragm disease in patients who underwent diaphragm resection and peritoneal stripping

Distribution of diaphragm disease	Diaphragm Resection n (%)	Peritoneal stripping n (%)
Peritoneal surface only	6 (19.4)	14 (36.8)
Invasion into fibrous/adipose tissue	9 (29.0)	14 (36.8)
Invasion into muscle	4 (12.9)	5 (13.2)
Invasion into/through pleural surface	8 (25.8)	0 (0.0)

Table 4: Surgical procedures and associated morbidity

	Diaphragmatic resection N=31 (36.5%)	Peritoneal stripping N=38 (44.7%)	Ablation / Minor resection N= 16 (18.9%)	P Value
Additional surgical procedures	n (%)	n (%)	n (%)	0.1780
Peritonectomy (abdominal/pelvic)	24 (77.4)	33 (86.8)	9 (56.3)	
Recto-sigmoid resection	20 (64.5)	26 (68.4)	11 (68.8)	
Appendicectomy	11 (35.5)	5 (13.2)	3 (18.8)	
Splenectomy	6 (19.4)	7 (18.4)	3 (18.8)	
Other bowel resection	6 (19.4)	7 (18.4)	1 (6.3)	
Lymphadenectomy	3 (9.7)	7 (18.4)	2 (12.5)	
Cholecystectomy	1 (3.2)	2 (5.3)	0 (0.0)	
Liver resection	1 (3.2)	1 (2.6)	0 (0.0)	
Distal pancreatectomy	1 (3.2)	1 (2.6)	0 (0.0)	
Gastric resection	1 (3.2)	1 (2.6)	0 (0.0)	
Highest grade** of complication	n (%)	n (%)	n (%)	0.640
None	13 (41.9)	10 (26.3)	4 (25.0)	
Grade 1	7 (22.6)	5 (13.2)	5 (31.3)	
Grade 2	6 (19.4)	17 (44.7)	5 (31.3)	
Grade 3a/3b	3 (9.7)	5 (13.2)	0 (0.0)	
Grade 4a/4b	1 (3.2)	1 (2.6)	1 (6.3)	

Grade 5	1 (3.2)	0 (0.0)	1 (6.3)	
---------	---------	---------	---------	--

** Grade as per the Dindo grading system [18].

Table 5: Details of grade 3 and 4 complications following diaphragm surgery

Grade 3 complications
Pneumothorax requiring chest drain and bronchoscopy
Pleural effusion requiring drain insertion
CPAP for respiratory failure
Return to theatre for wound closure
Return to theatre for drainage of pelvic abscess
Return to theatre for refashion of colostomy with drainage of parastomal haematoma
Return to theatre due to stoma necrosis
Grade 4 complications
Cerebral vascular accident
SIADH syndrome and acute renal failure
Return to theatre for stoma formation following failed anastomosis
Surgical intervention for intra-abdominal bleeding which necessitated a splenectomy

Table 6: Morbidity in patients following diaphragmatic surgery compared to matched controls

Highest grade of Complication	Diaphragmatic surgery n (%)	Matched controls with no diaphragmatic surgery n (%)	P Value
None	27 (31.8)	26 (30.6)	0.8728
Grade 1	17 (20.0)	18 (21.2)	
Grade 2	28 (32.9)	21 (24.7)	
Grade 3a/3b	8 (9.4)	12 (14.1)	
Grade 4a/4b	3 (3.5)	4 (4.7)	
Grade 5	2 (2.4)	4 (4.7)	